# Idiopathic intracranial hypertension: a possible association with Imatinib

**Anja M. Palmowski-Wolfe,[1] Eva Pape,[2] Thomas Baumann,[3] Margarita G. Todorova[1]**

**[1]University of Basel, Department of Ophthalmology; [2]University Basel, Department of Neurology, Basel; [3]Neurozentrum Bern, Bern, Switzerland**

## Abstract

Idiopathic intracranial hypertension (IIH) is characterized by an increased intracranial pressure in the absence of a tumor and in the absence of a venous thrombosis. Associated risk factors include obesity and several medications such as tetracyclines. We report a 60-year-old patient who developed IIH under treatment with imatinib. To our knowledge such a possible connection has not been reported in the literature, even though intracranial hypertension is now listed as a rare possible side effect of treatment with imatinib in the Swiss List of Medications Arzneimittelkompendium. It remains to be seen, if further case reports will support this observation.

## Introduction

Imatinib inhibits particular tyrosine kinases that are expressed excessively in certain carcinomatous diseases and also inhibits platelet-derived growth factor. It was introduced approximately a decade-and-a-half ago to treat chronic myeloid leukaemia (CML). In this disease a certain tyrosine kinase, encoded by the BCR-Abl gene transcript, is expressed and causes uncontrolled cell divisions through its excess activity. This process can be blocked with imatinib which results in a reduction of the number of pathologic tumor cells.[1] Meanwhile imatinib is also applied to treat patients with gastrointestinal stromal tumors.[1] Imatinib is the only FDA approved tyrosine kinase inhibitor for the treatment of patients with systemic mastocytosis, where a majority of patients excessively express the mast and stem cell growth factor receptor, SCFR or CD117, encoded by the KIT gene, and which has tyrosine kinase activity.[2] As imatinib has only been on the market for a relatively short time, with time, new side effects are being described.[1] We report a possible association between imatinib and Idiopathic intracranial hypertension (IIH).

## Case Report

A 60-year-old Caucasian female presented with blurred vision at our department of neurology. Her past medical history was remarkable for a systemic mastocytosis of more than 35 years, with possible gastrointestinal involvement, and with bone marrow involvement proven by histology. For the last 3 years, the mastocytosis was treated with imatinib, which is marketed by Novartis under the name of Glivec (imatinib ut imatinib mesilate) in Europe and under the name of Gleevec (imatinib mesilate) in the US. The patient also had obesity of more than 30 kg excess body weight (WHO III) and arterial hypertension.

On examination, her Snellen visual acuity in decimal equivalents was 0.7 in each eye. Chronic papilledema was present in both eyes, and as a consequence, there were already signs of chronic nerve fibre damage, notably disc atrophy (Figure 1). The optical coherence tomography demonstrated a superior temporal nerve fibre layer defect (Figure 2). This nerve fiber layer defect correlated with a bilateral caudal nasal visual field defect (Figure 3). Magnetic resonance imaging revealed enlarged optic nerve sheaths with increased filling on both sides and a partial empty sella, which had already been described 4 years previously (Figure 4). A thrombosis of the sinus veins was ruled out with magnetic resonance venography (Figure 5). On lumbar puncture an increased intracranial pressure (ICP) of 38.5 $cmH_2O$ was measured. The number of cells in the cerebrospinal fluid was normal ($0.3\times10^6$/L), and total protein was 349 mg/L.

In order to reduce ICP, the patient was started on oral acetazolamide 250 mg four times per day. Weight reduction was recommended and dietary training was provided, albeit with limited success. Under the hypothesis that imatinib might be associated with the increased ICP, the manufacturer of the imatinib was contacted. A closer association to imatinib could not be proven at the time. Nevertheless the patient was switched to nilotinib (Tasigna, Novartis), a second-generation tyrosine kinase inhibitor. Under these measures, the blurred vision went away and the visual acuity improved to 0.8 in the right eye and 1.0 in the left eye. Over a time period of one-and-a-half years, the visual fields showed no significant changes. When an attempt was made to discontinue diamox, blurred vision recommenced but then resolved again with oral acetazolamide. Acetazolamide was then switched to topiramate, an anticonvulsant that, among other presumed actions, inhibits the carbonic anhydrase enzyme and has an anorectic side effect. Under this treatment, the patient became free of symptoms and lost 3 kg over the course of 2 months.

Correspondence: Prof. Dr. Anja Palmowski-Wolfe, Universität Basel, Augenklinik, Mittlere Strasse 91, CH 4031 Basel, Switzerland.
Tel. +41.61.265.8722 - Fax: +41.61.265.8744.
E-mail: palmowskia@uhbs.ch

Key words: idiopathic intracranial hypertension, glivec, imatinib.

Received for publication: 30 May 2011.
Revision received: 30 September 2011.
Accepted for publication: 30 October 2011.


*Eye Reports 2011; 1:e13*
*doi:10.4081/eye.2011.e13*

## Discussion

IIH is a disease of unknown etiology. Obesity, especially of the lower body half, increases the risk of developing IIH. Medications such as tetracyclines have also been associated with this disease.[3] In rare cases, IIH has been described as a presenting symptom in CML, a myeloproliferative

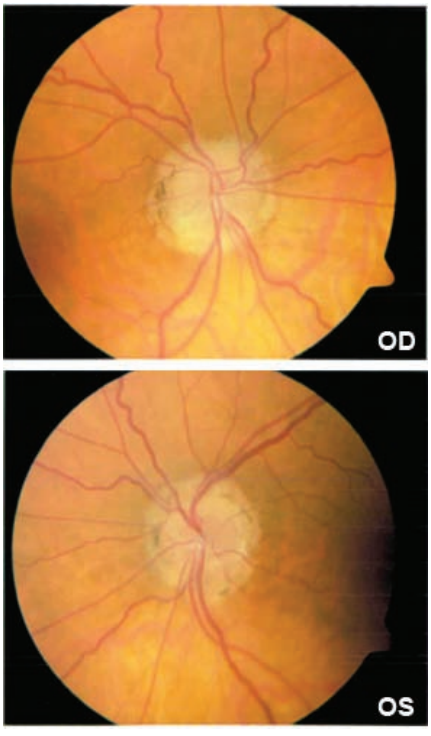


**Figure 1. Fundus photographs of the right and left optic nerve heads show the patient's chronic papilledema with a resulting slight disc pallor as a sign of beginning optic atrophy.**

disorder that results in an increase of leucocytes present in the bone marrow and blood. It has been postulated, that the very high white blood cell count in CML reduces the absorption of cerebrospinal fluid (CSF) into the sinuses, thus leading to IIH.[4,5] Mastocytosis is a rare disease that also leads to an increased production of cells, in this instance mast cells and their precursors.

In our patient, her mastocytosis was well controlled and, at the time where she developed IIH, there was no increased number of cells in her blood. Therefore, an increased hyperviscosity of the peripheral blood preventing resorption of CSF into the sinuses seems an unlikely cause of IIH in our patient. In addition, we have not found any reports in the peer-reviewed medical literature (using MEDLINE) that describe IIH in mastocytosis.

Imatinib is a recent drug which means, that with time, new side effects are being described.[1] In a search of the peer-reviewed medical literature (using MEDLINE), we have not found a reported association of imatinib and IIH. However, a non peer-reviewed anecdotal report revealed a possible connection in one individual who was on imatinib for 10 months and *ended up with pseudo tumor cerebri*.[6] In another non peer-reviewed literature document IIH is claimed as a potential rare side effect of imatinib, though no clinical case report, reference, or substantiation is provided.[7]

The pathomechnism by which imatinib might cause IIH is not clear. Weight gain from fluid retention has been reported as a frequent side effect of imatinib.[1] In fact, this fluid reten-

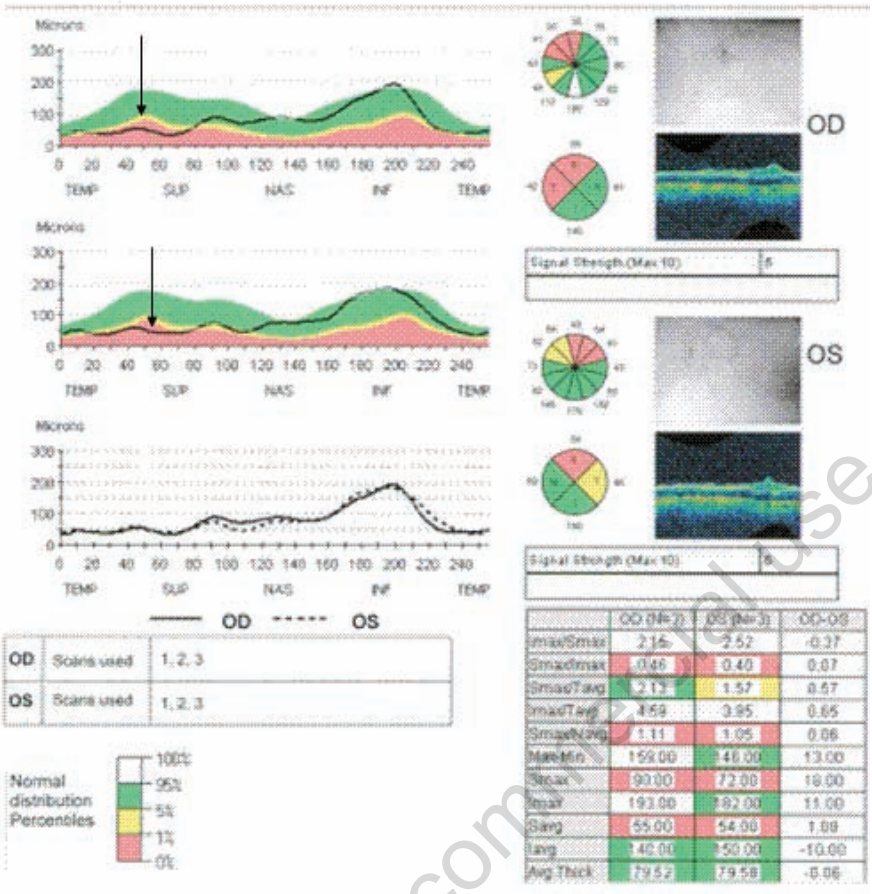


**Figure 2. The optical coherence tomography reveals superior temporal nerve fibre layer (NFL) loss. The black line demarcates the patient's NFL thickness for the right eye (top) and for the left eye (below). Reduced NFL thickness (marked by the black arrows) is indicated when this line deviates from the green area of normative values in to the red area.**

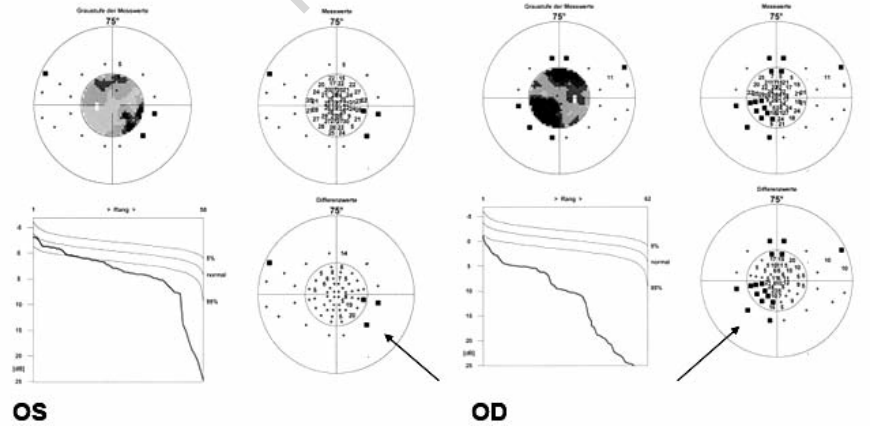


**Figure 3. The nerve fibre layer loss seen in Figure 2 correlates well with the visual fields obtained at that time. These show a nasal, more caudal field loss (black arrows) in the right eye more than the left eye.**

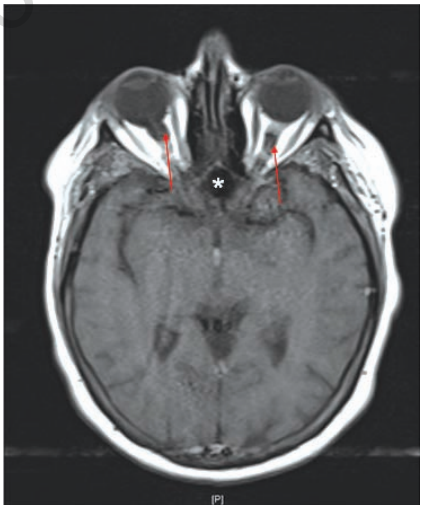

**Figure 4. Magnetic resonance imaging demonstrates enlarged optic nerve sheaths (red arrows) as well as a partial empty sella (asterisk).**

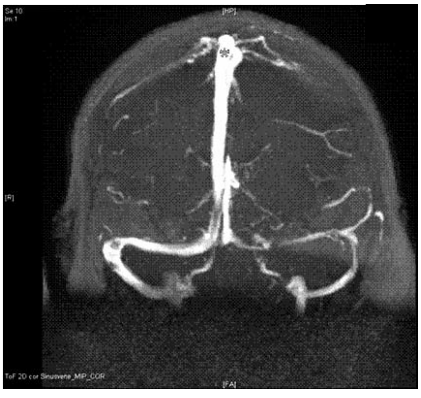

**Figure 5. The sinus veins are shown with contrast medium (asterisk). With this magnetic resonance venography a thrombosis of the sinus veins could be ruled out.**

tion can also occur in the brain. In 2002, Ebnöether, *et al.* reported 2 patients who developed cerebral edema under imatinib; in one of these patients, this cerebral edema occurred 6 months after the treatment was started. The authors explained the underlying pathomechanism as follows: imatinib inhibits platelet derived growth factor which may result in a decrease in interstitial fluid pressure and increase in capillary-to-interstitium transport.[8] In addition, imatinib may increase appetite and lead to weight gain from increased food intake, as in our patient who had gained 30 kg when started on imatinib.

An association between imatinib and IIH may thus exist either as a direct association or as an indirect association through induction of a weight increase. As such an association could not be ruled out, the patient was switched to nilotinib. Nilotinib is a second generation tyrosine kinase inhibitor that has a target profile similar to imatinib.[2] Even though it is not quite as successful as imatinib in the treatment of systemic masocytosis,[2] to our knowledge, IIH has so far not been associated with nilotinib. In the meantime, IIH has been included in the Swiss medical compendium as a possible side effect of imatinib. However, the Swiss medical compendium does not suggest a pathomechanism and also does not provide additional reasoning for this listing.

## References


1. Mughal TI, Schrieber A. Principal long-term adverse effects of imatinib in patients with chronic myeloid leukemia in chronic phase. Biologics 2010;4:315-23.
2. Ustun C, DeRemer DL, Akin C. Tyrosine kinase inhibitors in the treatment of systemic mastocytosis Leuk Res 2001;35: 1143-52.
3. Kapoor KG. More Than Meets The Eye? Redefining Idiopathic Intracranial Hypertension. Int J Neurosci 2010;120:471-82.
4. Abbot L, Mioneau G, Johnston D. An unusual cause of headaches and priapism in a teenager. Paediatr Child Health 2008;13: 299-301.
5. Falardeau J, Lee A. Chronic myeloid leukemia mimicking idiopathic intracranial hypertension. Neuro-Ophthalmology 2001;26:229-34.
6. Side Effects with Glivec. CMLSupport Chronic Myeloid Leukaemia Support Group. Available from: http://www.cmlsupport.org.uk/node/5984
7. Imatinib Side Effects. Drugs.com, Drug Information online. Available from: http://www.drugs.com/sfx/imatinib-side-effects.html
8. Ebnöether M, Stentoft J, Ford J, et al. Cerebral edema as a possible complication of treatment with imatinib. Lancet 2002; 359:1751-52.